The impact of microtechnologies in chemical and pharmaceutical production processes.

Barbara PIETERS a, Géraldine ANDRIEUX a, Volker HESSEL b,c, Holger LÖWE b, Jean Christophe ELOY a, Dana KRALISCH d, Jean JENCK e*

a YOLE Développement, Lyon (France)  
pieters@yole.fr andrieux@yole.fr eloy@yole.fr

b Institute of Microtechnology, Mainz (Germany)  
hessel@imm-mainz.de loewe@imm-mainz.de

c Technische Universiteit Eindhoven (The Netherlands)

d Friedrich-Schiller-Universität Jena (Germany)  
dana.kralisch@uni-jena.de

e ENKI Innovation, Sainte-Foy (France)  
jenck@enki2.com *speaker

Jean F JENCK et al, AIChE Microprocessing keynote (paper 23a), Orlando, 24 April 06
1. Innovation, an answer to the challenges of Sustainable Development

2. Process Intensification, a new paradigm in Chemical Engineering

3. Microprocessing for Process Intensification. Supply of microstructured components

4. Intensified flux of information (R&D) vs. intensified flux of material (Production)

5. Implementation in chemical processing

6. Challenge of cost efficiency; Capex and Opex Example: Kolbe-Schmitt synthesis

7. Perspectives
Microstructured components are available

**Micromixers**
Mixing from few ml/h up to 30 l/h

- IMM: Interdigital micromixer

**Micro Heat exchangers**
Maximum value of 700 W/m²K at an air flow rate of 75 l/min

- Heatric: Cross Flow Heat Exchanger

**Microreactors**
Combinaison of µHE and µmixers

- Mikroglas: Microreactor
Enabling Technology

Microchannels enable compact unit operations with high capacity per unit volume by reducing transport distances.

Microchannel

Characteristic dimension

~ 0.1-1 mm

~ 10-100 mm

Conventional
Bayer Technology Services - Ehrfeld

Cost: 400-500€ per module. 100 k€ for a complete microplant.

Module construction

Dainippon Screen

Jean F JENCK et al, AIChe Microprocessing keynote (paper 23a), Orlando, 24 April 06
Field constantly evolving in terms of materials and technologies developments but also in terms of players. New companies start activities, others stop or reposition their activities.

Ex: IMM, Velocys, BTS Ehrfeld, Microinnova, Syrris, CPC, Mikroglas, Heatric, Dai Nippon Screen, IMT...

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7. Perspectives
From R&D to production: scale-up or scale-out?
Microtechnologies products offers a solution in automation of sample preparation and analysis. Sample preparation represents today about 60% of analysis costs.
Example of microtechnologies based products leading to a reduction in drug discovery expenses:

### Yole Developpement Life Sciences IC report

<table>
<thead>
<tr>
<th>Example of biochips products</th>
<th>CodeLink microarray</th>
</tr>
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<tbody>
<tr>
<td><strong>Example of microfluidics devices</strong></td>
<td>Gyrolab Bioaffy™ CD microlaboratory</td>
</tr>
<tr>
<td><strong>Example of microfluidics devices</strong></td>
<td>Fluidigm TOPAZ™ Screening Chips</td>
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</table>

- **To highly parallelize tests** to analyze the whole genome (30,000 genes)
- Request **low sample volume**
- Request **low reagent volume**

- **104 parallel microstructures** conveniently fitting into the CD, each covering a surface area of 2 x 15 mm.
- Within the CD microlaboratory, samples are applied to affinity columns (10 nl volume) in defined volumes of 100 nanoliters.

- enable protein crystallization through nanoscale free interface diffusion.
- automated setup of experiments.
- screening 1, 4 or 8 samples against 96 reagents, respectively.
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5. **Implementation in chemical processing: a few selected EXAMPLES**

6. Challenge of cost efficiency; Capex and Opex Example: Kolbe-Schmitt synthesis

7. Perspectives
Degussa Demis: microstructured epoxidation reactor

Model synthesis:

H₂O₂(υap) + H₂O → H₃C⁻CH⁻CH₂

Features:
- Modular (unit operations, capacity)
- Multi-purpose (catalyst and reaction)
- Reaction under pressure possible
- Reactions in the explosive regime feasible

New developments

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A fine chemicals plant in a ‘shoe-box’

www.fzk.de  6 July 06, 2005

• Chemical production with FZK microstructured reactor at DSM Fine Chemicals GmbH in Linz, Austria.

• **Within 10 weeks more than 300 tons of high-value product.**

• Product yield increased compared to conventional processing

• Less raw material use and less waste generation, more process safety

• Micro-reactor dimensions: 65 cm
  290 kg heavy; 1700 kg/h liquid throughput; several 100 kW power

**Other announcements:**
Clariant (2005): 1000 t/a pigment plant.
Batch cryo to continuous process.
Towards bulk chemicals.

- 30,000 l/h
- Bulk chemicals within reach

5kW microstructured fuel processor
autothermal reforming of iso-octane

Jean F JENCK et al, AIChe Microprocessing keynote (paper 23a), Orlando, 24 April 06
Radical polymerization

Plant running at industrial site of Idemitsu Kosan

Dr. Takeshi Iwasaki (MCPT)
Proceedings IMRET 8, Atlanta, April 2005.
Nitroglycerin microstructured pilot-plant (Xi’an, China)

investment ~5 M €

- Nitroglycerin production on a pilot plant level (15 kg NG; >100 l/h solution)
- Manufactured nitroglycerin used as medicine for acute cardiac infarction
- Product quality on highest grade
- Plant to operate safely and fully automated
- Environment protection by advanced waste water treatment & closed cycle

Chemie Ingenieur Technik, May 2005
Volume 77 (5)
10(+1) microreactor systems cost ~1.5 M$ per reaction stage, compared with lab-scale systems that can range between 20 and 200 k$.

Microreactor capacity on a contract basis: a commercial, large-scale, multiproduct plant near Leipzig, by mid-2006
• produce high added value chemicals (niche applications) with a range from 1 kg to 100 kg for pharmaceuticals
• Synthacon started production for multipurpose 20 t/a.

Sigma-Aldrich installed a standard Cytos in Buchs. The system has a list price of ~190 k$.

16 pharmaceutical and fine chemicals producers are interested in the technology [..]
Many of Sigma-Aldrich's catalog products are produced under typical lab conditions in flasks of up to 20 L. Of the 2 000 compounds in this portfolio, about 800 could be produced in microreactors with little or no process modification.
VALUE-ADDED CHAIN IN THE FIELD OF CHEMICAL ENGINEERING

Benchmarking
- Bronkhorst MFC: 5 k€
- Commercial Lab Evaporator: 15 k€
- Industrial Pilot: 450 k€
- Nitroglycerin Production Plant: 4-5 Mio€

Chemical Processes
- Production Plants
- Pilot Plants
- Laboratory Plants
- Pilot Apparatus Production Apparatus

Process & plant engineering
- Reactor engineering
- Microstructures / Accessoires
- Laboratory Apparatus
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5. Advantages and hurdles for implementation in chemical processing


   - Aniline (CMD, Yole)
   - Hydrogen peroxide (UOP)
   - Fine chemicals (Lonza)
   - Process incentives (D.Kralisch)
   - Kolbe-Schmitt synthesis (IMM)

7. Perspectives
Aniline is a highly exothermic process with associated disadvantages

Current Practice

Issues for tubular fixed bed:
- Reduction in performance
- Unloading & loading of catalyst
- Frequent regeneration
- Highly exothermic

MRT Solution

- Immobilized catalyst
- Lower hydrogen recycle rate
- Avoidance of by-products through temperature control
- No loading & unloading of catalyst
- Downtime significantly reduced

Variable Cost Analysis for a 50 000 t/a production
savings > 210 000 US$ per year….

only 5 US$ per ton !?
### Aniline by microprocessing $\text{H}_2+\text{NB}$

**Source:** CMD International AG, 2002

<table>
<thead>
<tr>
<th>Fixed bed</th>
<th>Costs (US$\text{/year})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading of catalyst (pressure drop is particularly critical for tubular reactors) by specialized companies with long downtime</td>
<td>Loading &amp; unloading cleaning ~260 000 US$ extra charge of catalyst (± 12.5 t) 660 000 US$</td>
</tr>
<tr>
<td>Regeneration sequence at regular intervals (drop in activity &amp; selectivity over time)</td>
<td></td>
</tr>
<tr>
<td>Excess of hydrogen (recycle NB:$\text{H}_2 = 1:9$) use of sulphuric acid (20 kg per t of aniline)</td>
<td></td>
</tr>
<tr>
<td>Unloading of de-activated catalyst and disposal of catalyst by specialized companies (EU approved)</td>
<td>??</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>&gt;&gt; 660 000 US$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Microprocessing</th>
<th>Costs (US$\text{/year})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better process control, less steep $\Delta T$, less coke formation, less by-products</td>
<td>Loading &amp; Unloading catalysts (~160 000 to 250 000 US$)</td>
</tr>
<tr>
<td>Reduction of Sulphuric Acid</td>
<td></td>
</tr>
<tr>
<td>Reduced downtime $\Rightarrow$ Increased productivity</td>
<td></td>
</tr>
<tr>
<td>Faster regeneration</td>
<td>Prolonged runs/lifetime 200 000 US$</td>
</tr>
<tr>
<td>No specialised companies for loading &amp; unloading of catalyst</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>360 000 to 450 000 US$</td>
</tr>
</tbody>
</table>
Direct hydrogen peroxide by H₂+O₂ in explosive regime
Basic engineering of a 160 000 t/a plant


<table>
<thead>
<tr>
<th>O₂:H₂ ratio</th>
<th>3</th>
<th>1.50</th>
<th>1</th>
<th>6.79</th>
<th>1.89</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure (psia)</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>1450</td>
<td>1450</td>
</tr>
<tr>
<td>Conversion</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Selectivity</td>
<td>0.85</td>
<td>0.8</td>
<td>0.65</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Yield</td>
<td>0.765</td>
<td>0.72</td>
<td>0.585</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>TOTAL COST ($ MM)</td>
<td>68.27</td>
<td>61.54</td>
<td>64.00</td>
<td>140.07</td>
<td>98.85</td>
</tr>
</tbody>
</table>

**Projected Production Cost (¢/lb)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw Material less Byproducts</td>
<td>4</td>
</tr>
<tr>
<td>Consumables</td>
<td>2</td>
</tr>
<tr>
<td>Utilities</td>
<td>3</td>
</tr>
<tr>
<td>Labor/Maintenance</td>
<td>1</td>
</tr>
<tr>
<td>Overhead</td>
<td>1</td>
</tr>
<tr>
<td>Capital Recovery</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
</tr>
</tbody>
</table>
Classification of 86 reactions campaigns carried out at Lonza

- Type A reactions: very fast, < 1 s; mixing controlled
- Type B reactions: rapid, 1 s to 10 min; kinetically controlled
- Type C reactions: slow, > 10 min; safety and quality issues

- 50% of the reactions to benefit from a continuous process
- 63% not suited to current micro reactors due to solid carriage

**OPEX costs**

- Raw material costs are 30-80%
- Higher product yield and quality may have a significant impact
- Automated process reduces QA/QC and labor costs

**CAPEX costs**

- Low scale-up coefficient ($n=0.3$)
- Micro-reactor costs as high or higher


Jean F JENCK et al, AIChe Microprocessing keynote (paper 23a), Orlando, 24 April 06
Microreactor process cost incentives

*Coarse costs estimate based on a few similar estimated and real-case production scenarios in the field of fine chemicals, averaged to one plot*

*Only considering the reaction to the crude product; no purification*

Productivity: 100 t/a (8,000 h equiv)
Annual earnings: 300 k€
Return-on-invest: ~7 years
Microreactor process cost incentives

- The costs for micro structured reactors 10-15% ; catalogue ware
- Other costs are due to standard engineering (~45%) and peripherals (~40-45%)
- The latter share may be notably reduced, when relying on existing equipment (‘plant upgrading’)

Installation costs
- equipment installation
- electrical equipment and electrical connection
- control materials and control installation
- insulation

Dana Kralisch

Friedrich-Schiller-University Jena
Faculty of Chemistry and Earth Science
Institute for Technical and Environmental Chemistry

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Microreactor process cost incentives: example of the high-T,P Kolbe-Schmitt synthesis

V. Hessel, C. Hofmann, P. Löb, J. Löhndorf, H. Löwe, A. Ziogas

High p,T

- Pressure: 40-70 bar
- Temperature: 100-220°C
- Reaction time: 4 – 390 s

- Reduction of reaction time by ~2000
- Increase in space-time yield by factor 440
- Increase in productivity by factor 4
Advanced rig for process optimization of the KOLBE-SCHMITT synthesis

**Second generation rig**
- Mixer 2 feeds
- Heat exchangers for pre-heating + quenching
### Overview: relationship between costing and microreactor operation

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Plant Description</th>
<th>Costing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base case: high-p,T</strong></td>
<td>µ-REAC PLANT – 1 reactor; 4.4 t/a; 2 l/h</td>
<td>92.10 € / kg</td>
</tr>
<tr>
<td></td>
<td>45% selectivity; 200°C / 40 bar (‘high-p,T’)</td>
<td></td>
</tr>
<tr>
<td><strong>Selectivity</strong></td>
<td>µ-REAC PLANT – 1 reactor; 4.4 t/a; 2 l/h</td>
<td>78.43 € / kg</td>
</tr>
<tr>
<td></td>
<td>70% selectivity; 200°C / 40 bar (‘high-p,T’)</td>
<td></td>
</tr>
<tr>
<td><strong>External numbering-up</strong></td>
<td>µ-REAC PLANT – 10 reactors; 44 t/a; 20 l/h</td>
<td>57.47 € / kg</td>
</tr>
<tr>
<td></td>
<td>45% selectivity; 200°C / 40 bar (‘high-p,T’)</td>
<td></td>
</tr>
<tr>
<td><strong>Intensify by high-p,T</strong></td>
<td>µ-REAC PLANT – 1 reactor; 44 t/a; 20 l/h</td>
<td>56.95 € / kg</td>
</tr>
<tr>
<td></td>
<td>45% selectivity; 200°C / 40 bar (‘high-p,T’)</td>
<td></td>
</tr>
<tr>
<td><strong>Without high-p,T</strong></td>
<td>µ-REAC PLANT – 1 reactor; 0.01 t/a; 0.005 l/h</td>
<td>17352.52 € / kg</td>
</tr>
<tr>
<td></td>
<td>45% selectivity; 100°C / 1 bar</td>
<td></td>
</tr>
<tr>
<td><strong>Bench-marking</strong></td>
<td>BATCH-REACTOR PLANT – 1 l; 0.27 t/a</td>
<td>985.18 € / kg</td>
</tr>
<tr>
<td></td>
<td>45% selectivity; 100°C / 1 bar (‘Reflux’)</td>
<td></td>
</tr>
<tr>
<td><strong>Bench-marking</strong></td>
<td>BATCH-REACTOR PLANT – 10 l; 2.7 t/a</td>
<td>107.05 € / kg</td>
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<td>45% selectivity; 100°C / 1 bar (‘Reflux’)</td>
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Perspectives: 1- opportunities for microprocessing in intensified formulation processes

in FINE CHEMICALS and ADVANCED MATERIALS

➔ product engineering by microprocessing:

- sharpening property distribution (MW, mean particle diameter, size, any property)
- challenge: high Peclet # (RTD due to laminar flow)

Examples:
- organic nanoparticles (paper 98a Fuji)
- ultrafine powders (papers 84a EPFL TechPowder and 98e Microinnova)
- block copolymers (paper 62d ULP Strasbourg)
- complex emulsions (paper 140g Unilever)
- emulsification modules (paper 140a Velocys)
from steam reforming to emulsification!
Product quality: homogeneity in solid formulation

Precipitation of copper oxalate

The micromixer is integral part of a Segmented Flow Tubular Reactor (SFTR)
Mono-disperse silica nanoparticles generated by a segmented flow microreactor

Microchemical Synthesis Colloids

- Oxide 10nm-1µm particles of SiO₂, TiO₂, etc.
- Wide range of applications: pigments, catalysts, electrochromic/photochromic coatings, foods, health-care products etc.

Perspectives: 2- eco-efficiency of microprocessing need for quantitative assessment

Benchmarking for exergetic efficiency

Microstructured methanol fuel processor


Breakdown of the cumulative energy demand of the scenarios “batch” and “worst case continuous” mode in single modules

D. Kralisch, K. Kreisel  

Jean F JENCK et al, AIChe Microprocessing keynote (paper 23a), Orlando, 24 April 06
Perspectives: 3- Market segmentation of microprocessing

Currently an emerging market at its daybreak.

Microprocessing development will follow molecule life cycle

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<td>Small volume production</td>
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Perspectives: 3- Market segmentation of microprocessing

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Key drivers for microreactor market growth

Chemistry:
- New technology to develop and produce very high quality molecules in fine chemicals
- High end differentiation of some chemical companies in a competitive environment where China is getting a leading position in some market segments
- Higher production yield and enhanced safety conditions.
- MRT could push the change from batch to continuous flow process

Pharmaceuticals:
Same drivers plus Specificity of pharmaceuticals:
- New reaction conditions leading to new drugs
- Increase in drug development pipeline rentability – more molecules will go through the toxicological testing (Phase I to IV)
Perspectives: global conclusion

Technology validation still to be assessed. Validation by economical benefit? OR a 'rush-to-be-second' and not so many excuses anymore not to use it?

Decisive for sustainable chemistry, new routes reconsidered. Also emerging in the pharmaceutical industry. Useful for on-site applications (cosmetics, drugs, testing).

Engineering methodologies required!